DOCKET NO: 291385US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
LUCA RAMPOLDI, ET AL	: EXAMINER: SULLIVAN, D.D.
SERIAL NO: 10/581,367	:
FILED: JUNE 2, 2006	: GROUP ART UNIT: 1616

FOR: PHARMACEUTICAL PREPARATION CONTAINING GABAPENTIN:

DECLARATION UNDER 37 C.F.R. 1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

Now comes Luca Rampoldi who deposes and states that:

1. I am a graduate of University of Milan and received my degree in the field of Chemistry and Pharmaceutical Technology , in the year 1997.

2. I have been employed by Zambon Group S.p.A. for 6 years in the field of Pharmaceutical Technology.

3. I am a named inventor of the above-identified application.

4. I understand the English language or, at least, that the contents of the Declaration were made clear to me prior to executing the same.

5. The following experiments were carried out by me or under my direct supervision and control.

6. Formulation study

Introduction

The aim of the development was to obtain a formulation for a finished product with physical and pharmaceutical characteristics similar to the marketed product.

Study rationale

For the preparation of high dosage strength gabapentin tablets the following factors must be taken into account:

- the physical properties of gabapentin powder which, in high dosage, have a decisive influence on the physical characteristics of the final powder mixture and the tablets derived thereof.
- Conservation of the form II crystalline structure of gabapentin
- The lactam derivative (gabapentin degradation product) must be maintained within the limit 0.4% which is considered tolerable for human use.
- Dimensions and weight of the tablets are to be kept within acceptable limits in order that the drug product is not difficult to swallow.
- Explosive nature of gabapentin in dry compacting processes

The initial development took into consideration the following technological approaches:

• Direct compression

Preliminary tests with a wide variety of excipients demonstrated the difficulties of obtaining gabapentin tablets with acceptable characteristics.

• Wet granulation

The trials gave a product with the hydrated form of gabapentin as well as an increase of the degradation product (lactam derivative; see paragraph 7 below).

• Melt granulation

As alternative to the wet granulation process a melt granulation was developed in order to obtain a granulate suitable for the production of both 600 and 800 mg tablets.

This type of process presented the following advantages:

- elimination of the use of water so avoiding the degradation of the active substance and its potential transformation to the hydrated form. Consequently the gabapentin is maintained in the polymorph II form
- a smoothly flowing, compressible granulate is obtained
- limited amounts of excipients are required
- use of well known and widely employed excipients

Formulation studies

A granulate was formulated to satisfy the above mentioned requirements with the aid of:

- a melt granulating agent: macrogol 4000
- a disintegrant: starch, pregelatinized

Investigations were carried out, as detailed below, by various techniques (DSC, FT-IR, FT-Raman spectrometry) to demonstrate the absence of any interactions between the active and the excipients and also that gabapentin maintains the polymorph II form after the granulation process.

• DSC analysis.

In particular the following samples were subjected to DSC analysis.

- Gabapentin starting material
- Macrogol 4000
- Gabapentin and macrogol, co-melted
- Granulate of gabapentin, macrogol 4000 and pregelatinized starch (batch 038/03)
- Mixture of gabapentin and pregelatinized starch (1: 1)
- Neurontin 800 tablet (powdered).

The respective spectra are shown in the figures identified as Figures 4-9 in this paragraph.

The thermograms of the granulate and of gabapentin co-melted with macrogol show that the active component remains in the polymorph II form and that there is no apparent evidence of interaction with the other ingredients.

• FT-IR analysis

The same samples tested by DSC were analyzed by FT-IR spectroscopy to check for any formation of covalent bonds. The spectra reported in the figures identified as Figures 10-17 in this paragraph show no evidence of the presence of new bonds in the granulate or in the co-melted gabapentin-macrogol 4000.

• FT-RAMAN analysis

The potential influence of macrogol 4000 on the crystalline form of gabapentin was investigated by FT-RAMAN spectroscopy. The spectra obtained, reported in the figures

identified as Figures 14, 15, 16 of this paragraph, do not show evidence of changes in the crystalline structure of gabapentin which remains in the polymorph II form both in the granulate and in the co-melted gabapentin-macrogol 4000.

Figure 4 : Gabapentin starting material – DSC thermogram

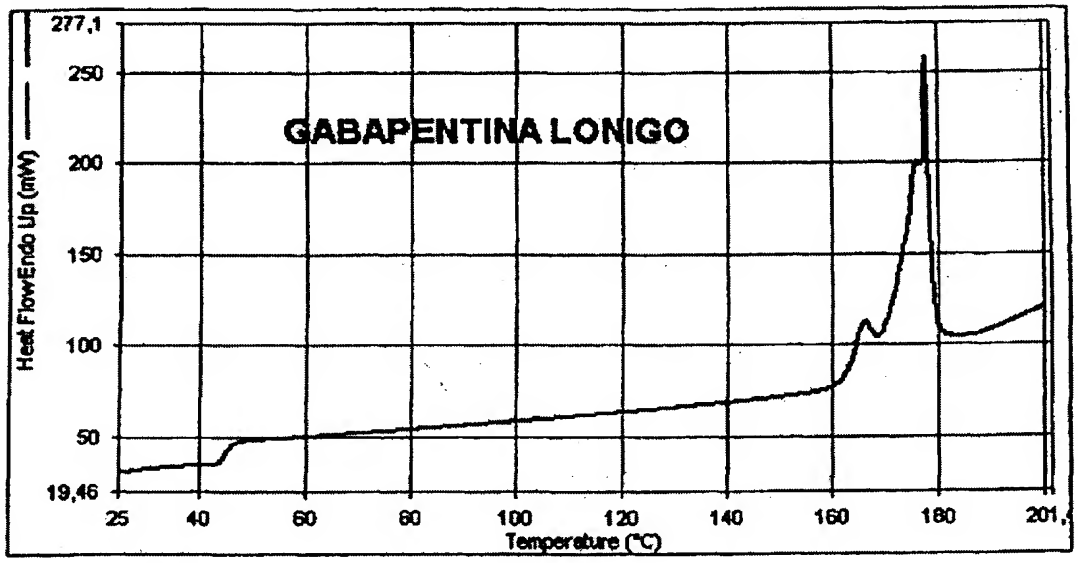


Figure 5 _ Macrogol 4000 – DSC thermogram

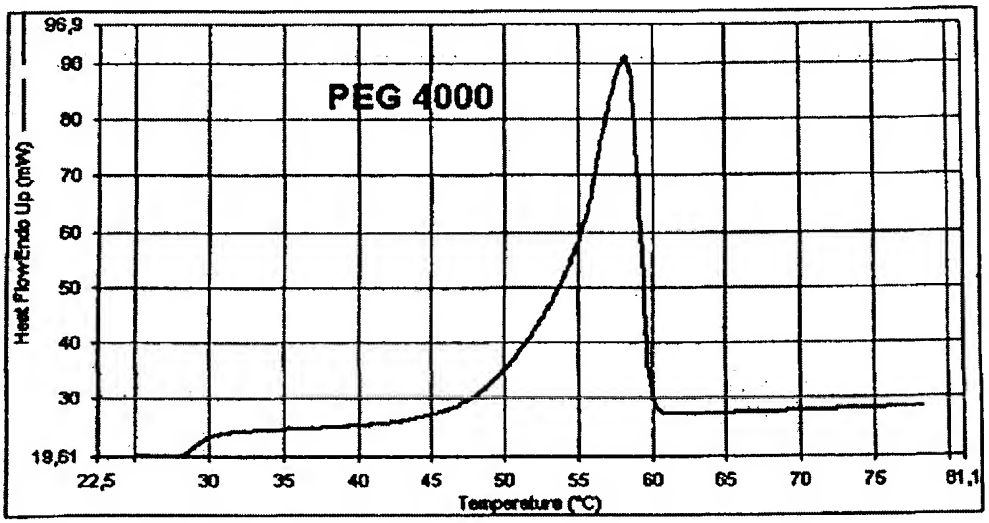


Figure 6 : Gabapentin Macrogol 4000 co-melted – DSC thermogram

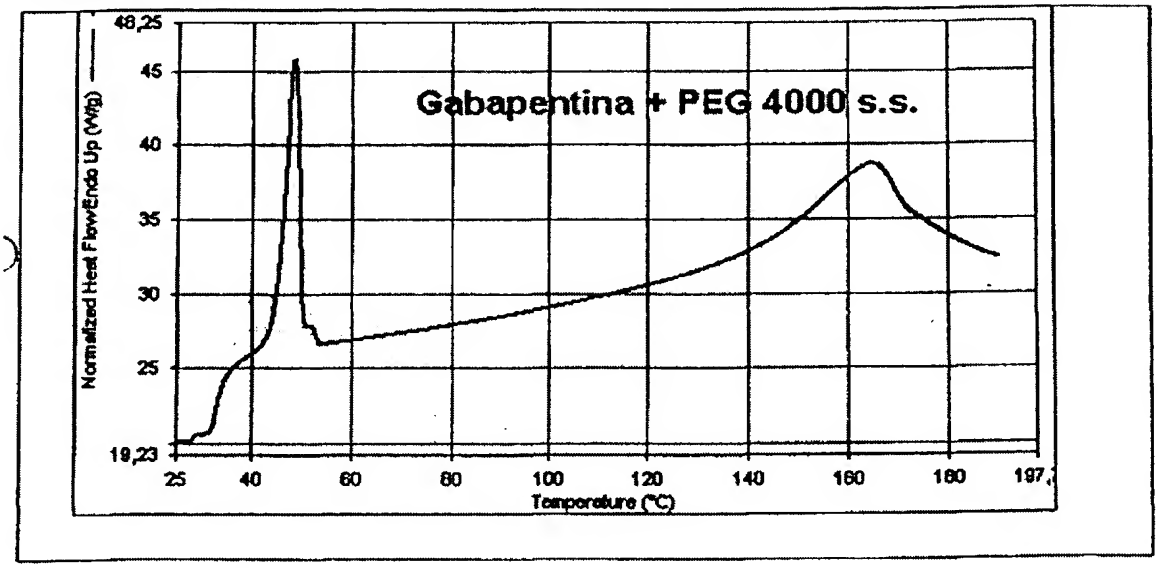


Figure 7 : Granulate of gabapentin, macrogol 4000 and pregelatinized starch – DSC thermogram

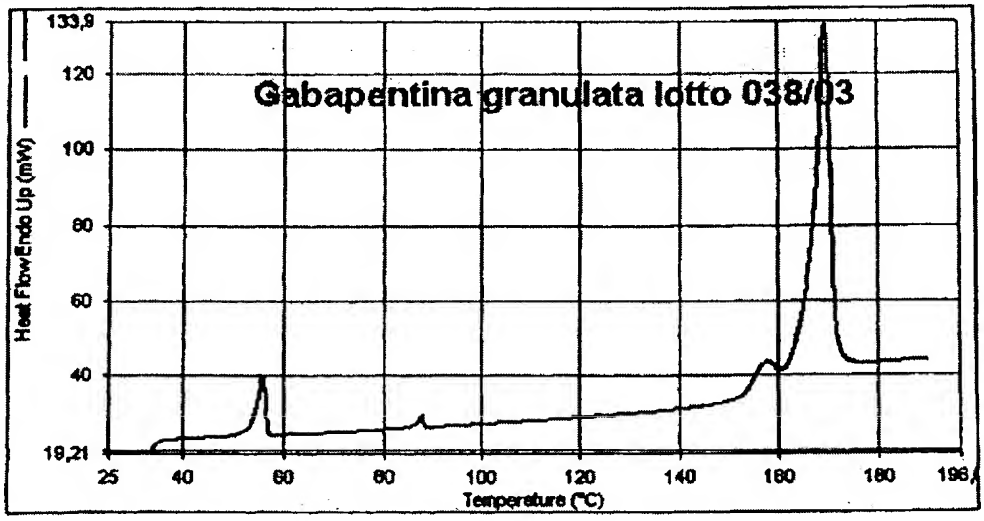


Figure 8 : Gabapentin and pregelatinized starch – DSC thermogram

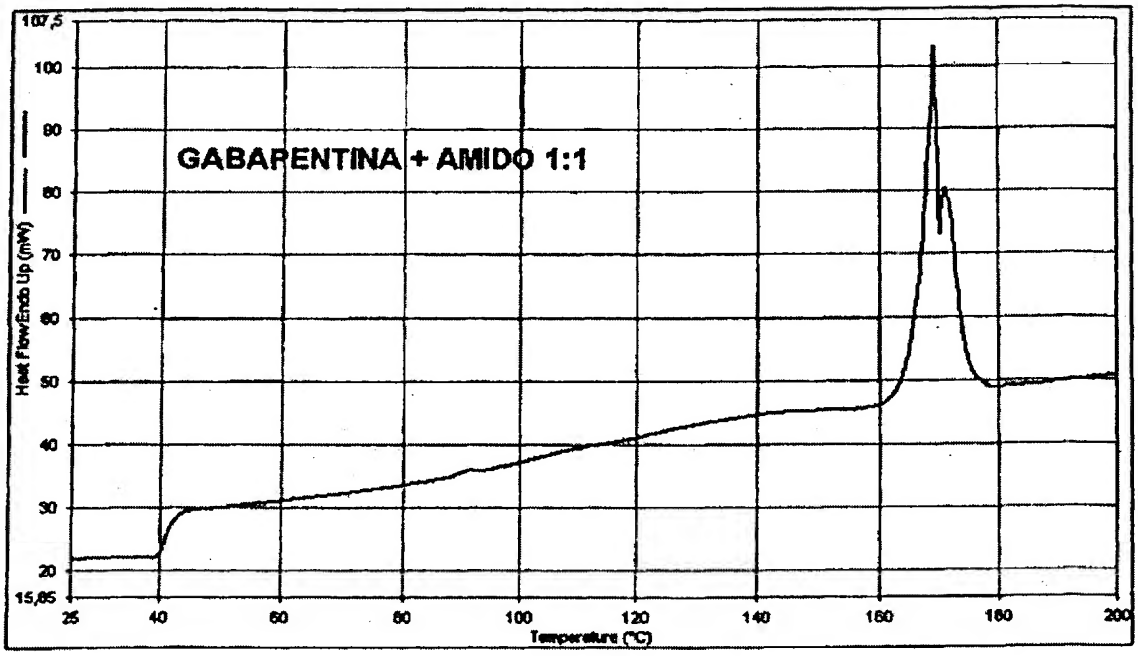


Figure 9 : Neurontin tablets (powdered)

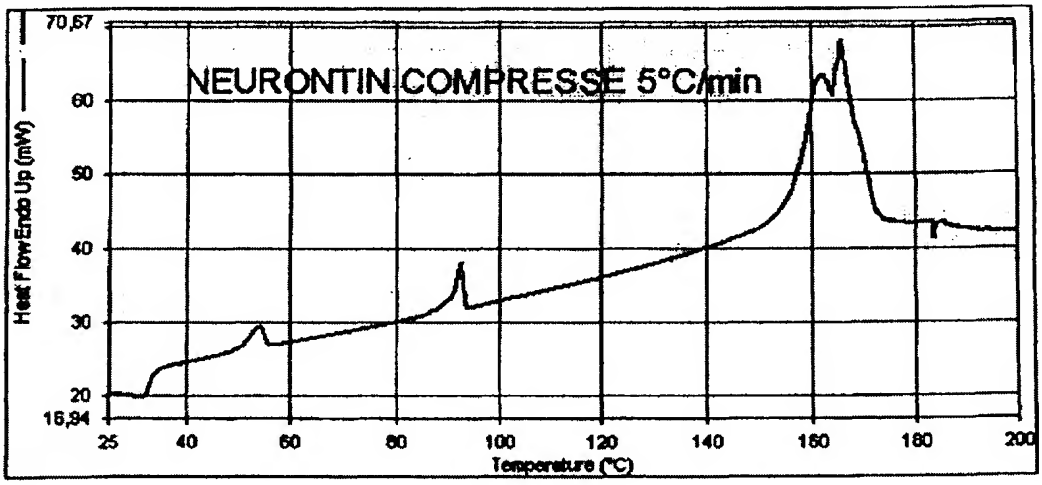


Figure 10 : FT-IR spectra : Gabapentin (bulk) (upper)
Gabapentin-macrogol 4000 co-melted (lower)

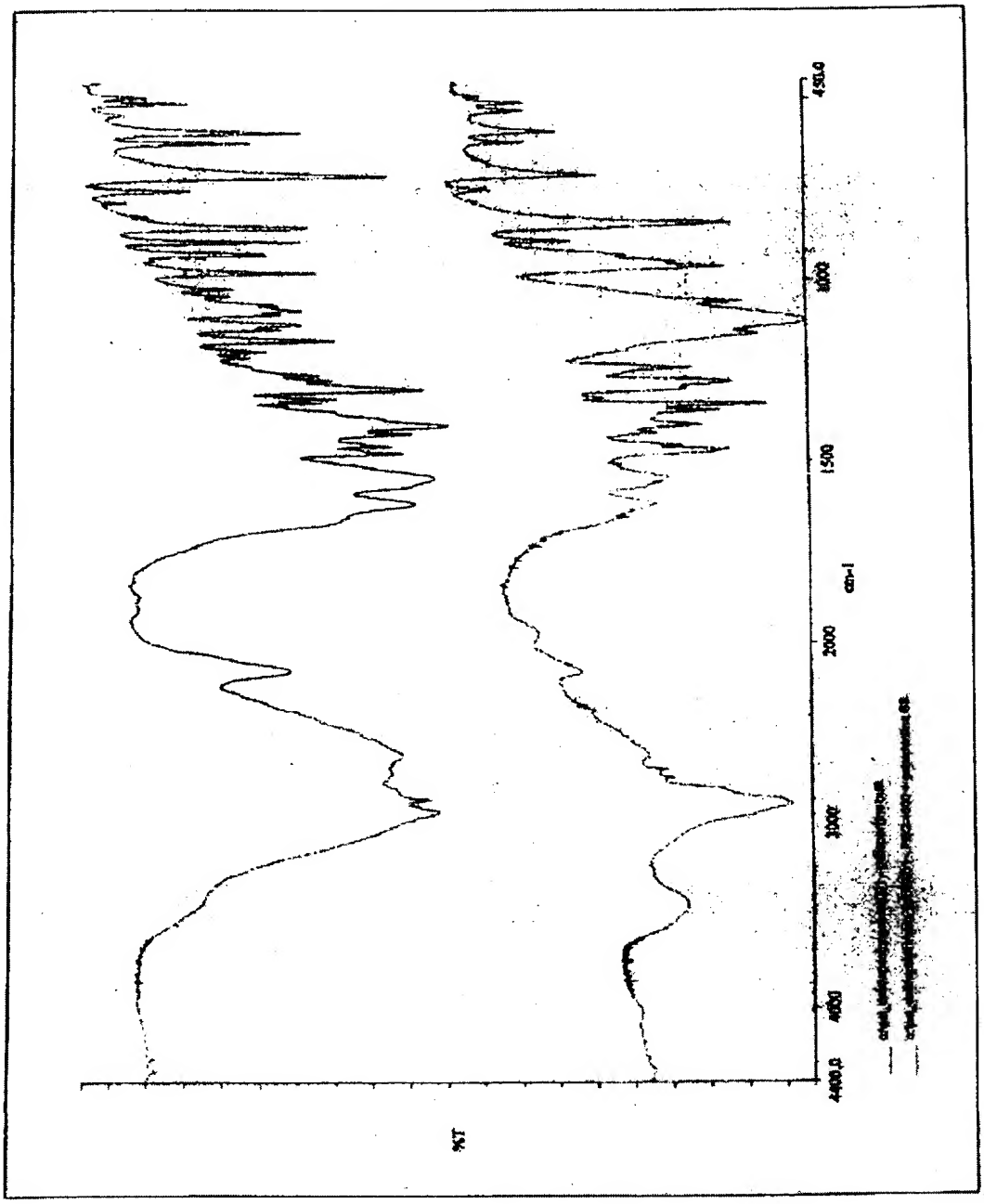


Figure 11 : FT-IR spectrum : Gabapentin (bulk)

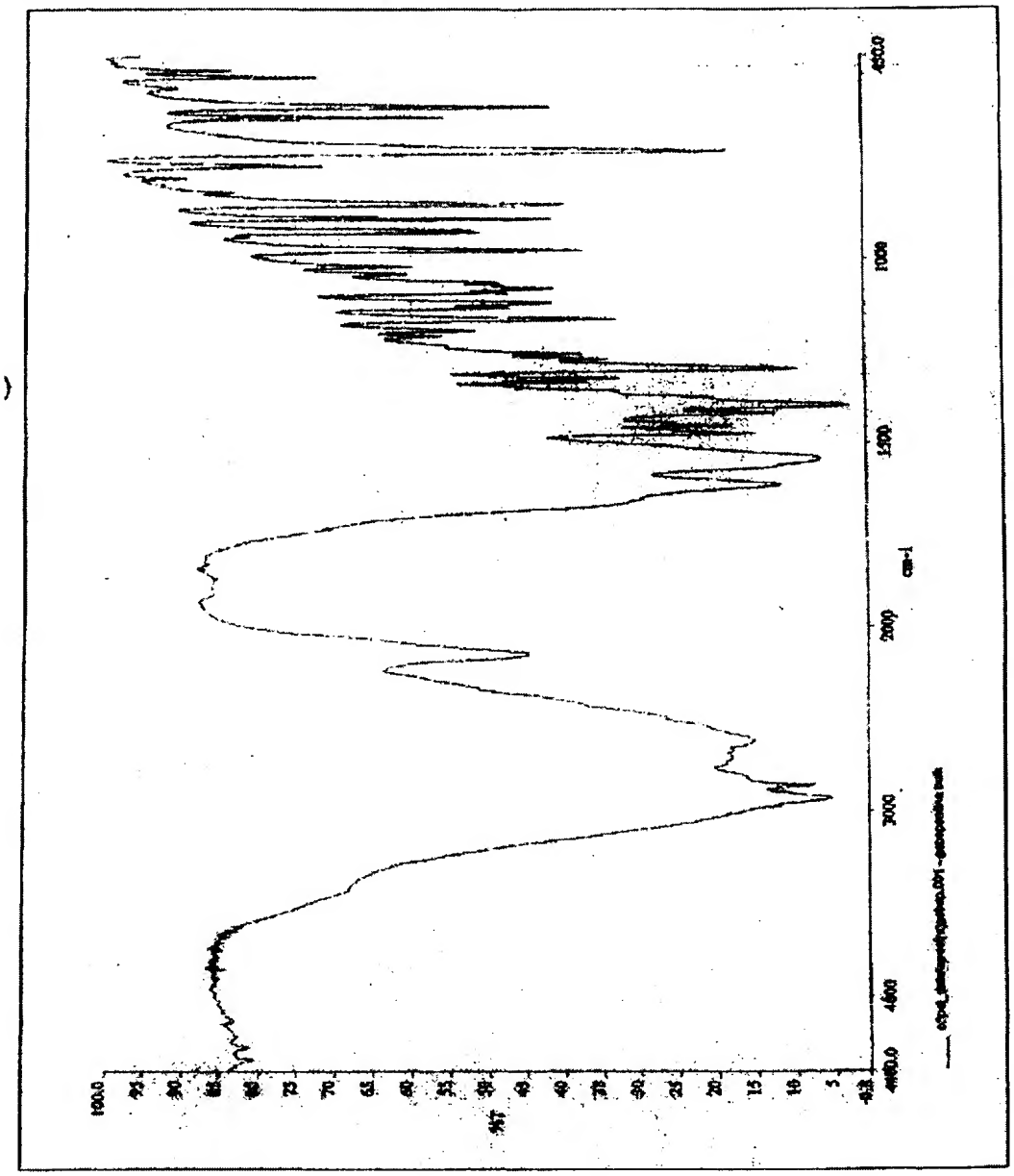


Figure 12 : FT-IR spectrum : Macrogol 4000

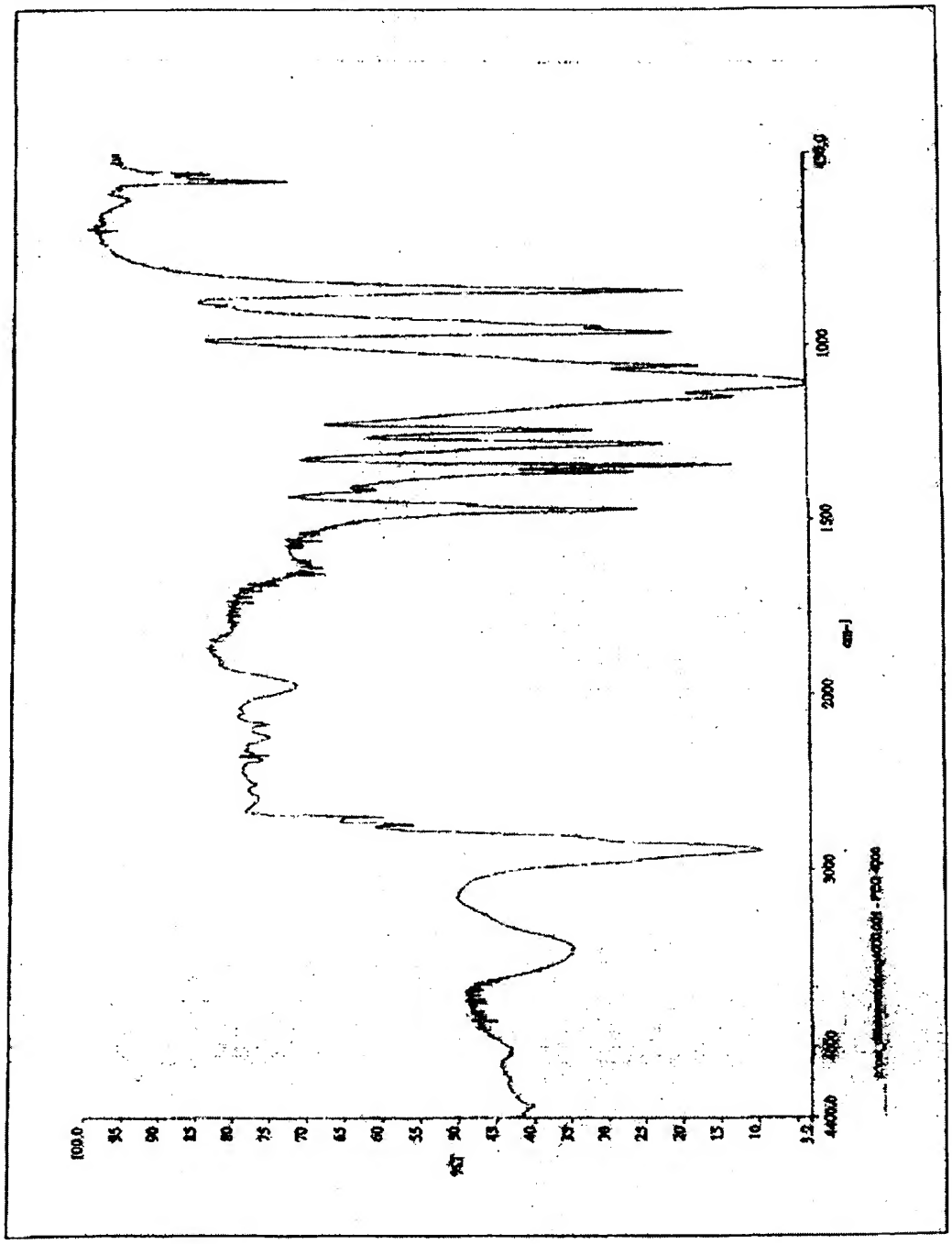


Figure 13 : FT-IR : Gabapentin – Macrogol 4000 co-melted

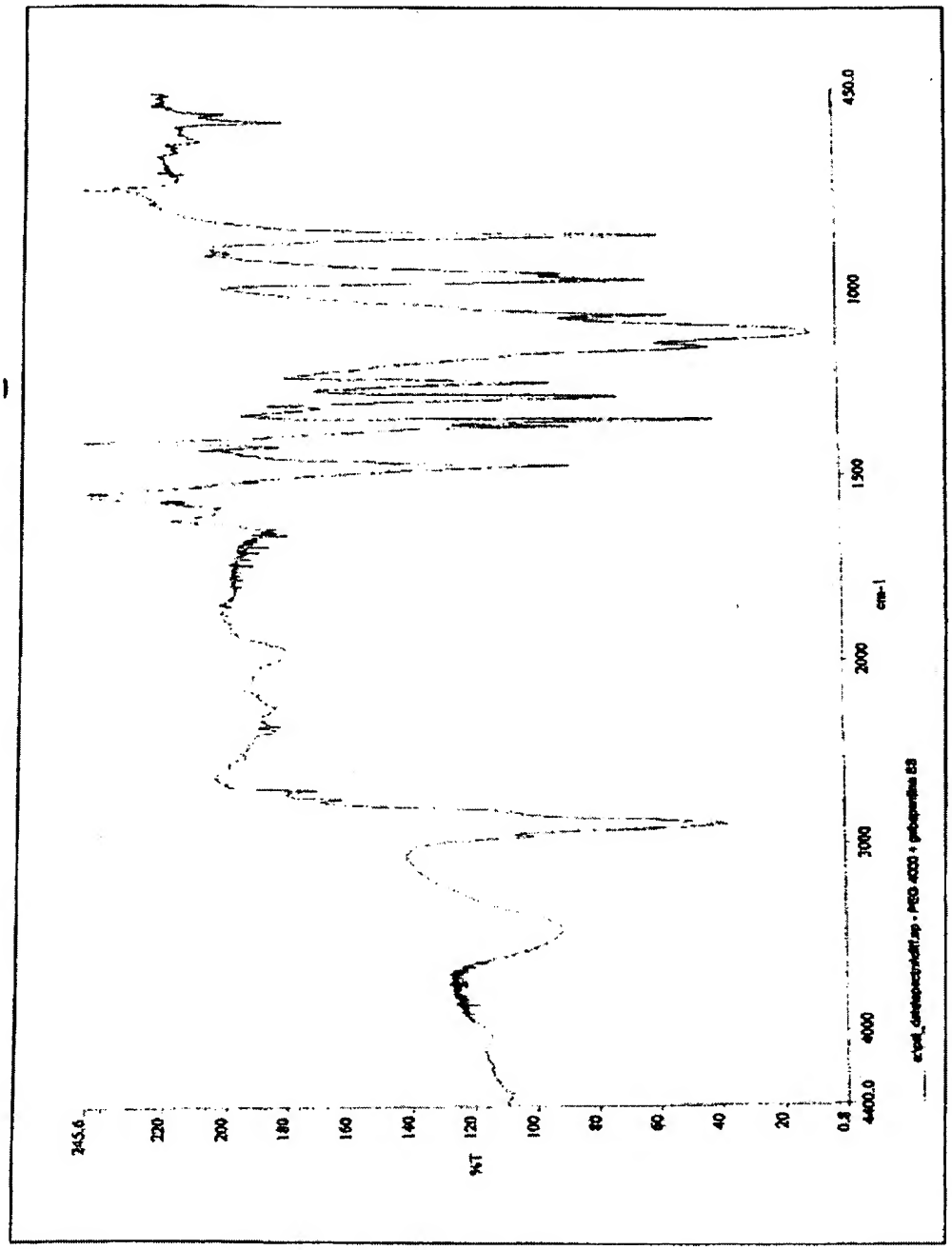


Figure 14 : FT-IR : Gabapentin-macrogol 4000- pregelatinized starch Granulate

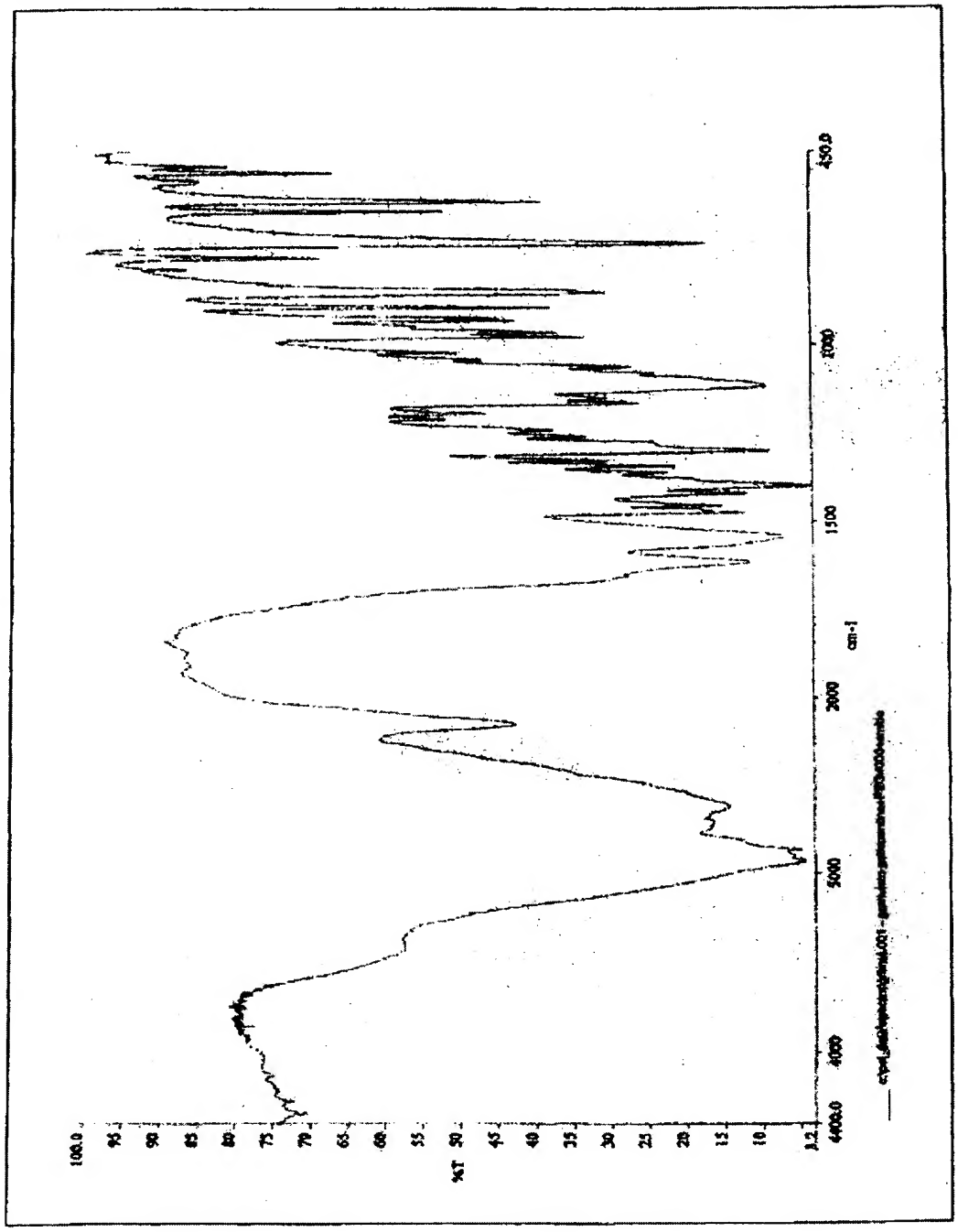
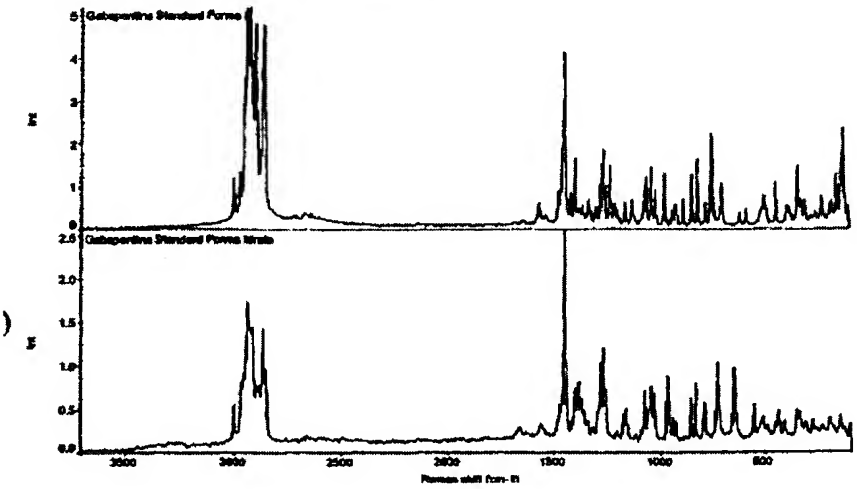
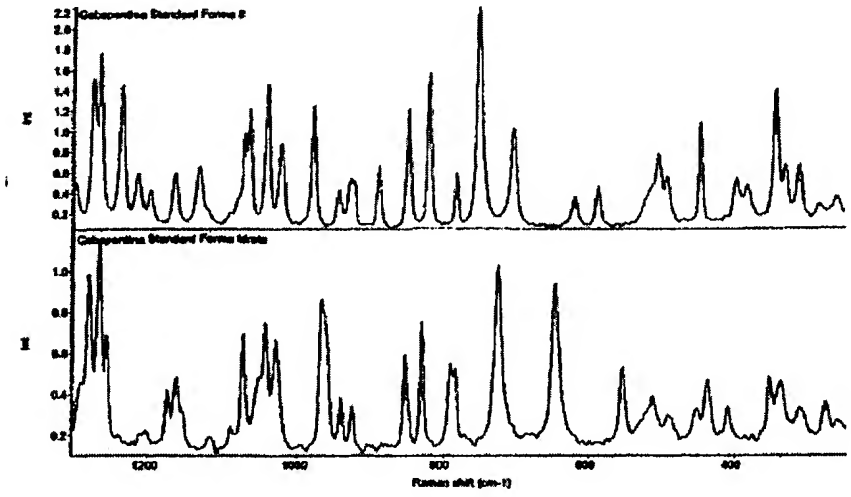


Figure 15 : FT-RAMAN spectra (in descending order)
Gabapentin polymorph II standard
Gabapentin hydrate standard



The differences in the Raman spectra are considerable especially in the range between 1300 and 250 cm^{-1}.



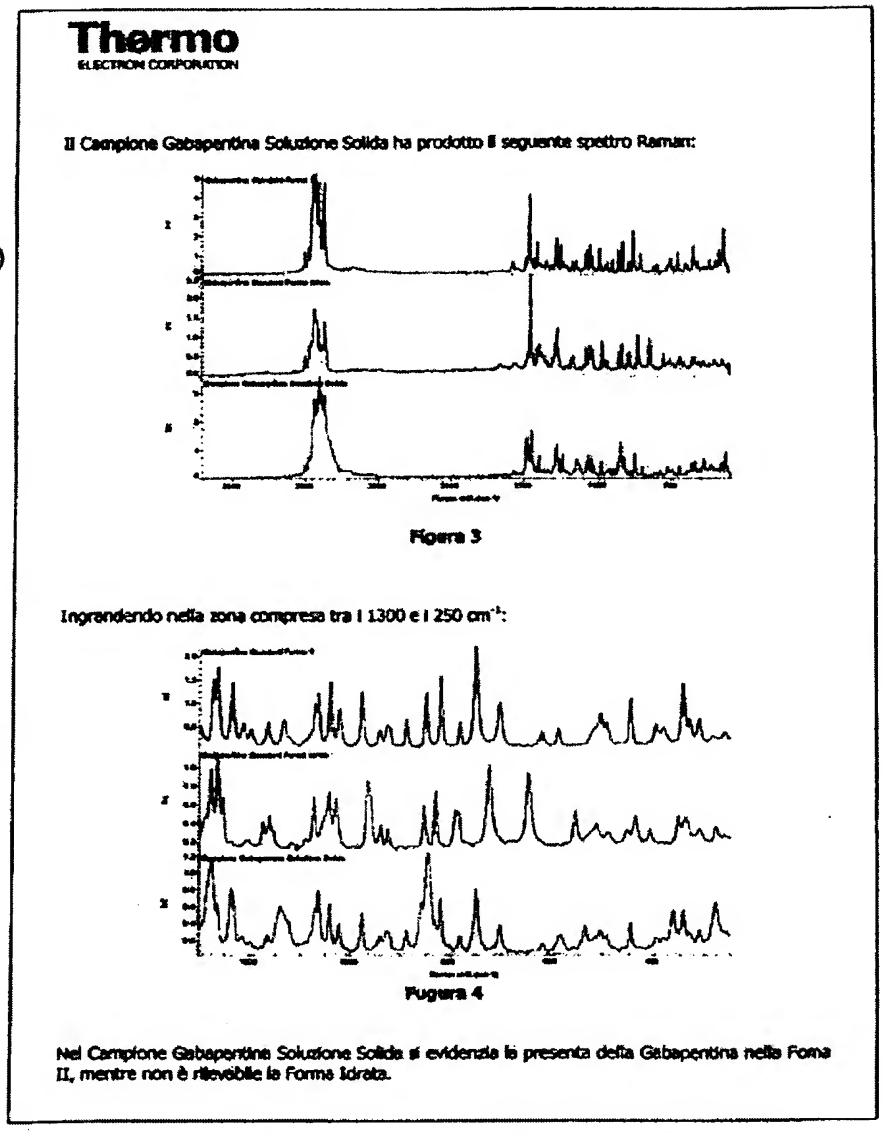
The considerable differences of the spectra of the two polymorphic forms of gabapentin permit the easy detection of the presence of one of the two forms in a sample.

Figura 16 : FT-RAMAN spectra (in descending order)

Gabapentin polymorph II standard

Gabapentin hydrate standard

Gabapentin-macrogol 4000 co-melted



Note : In gabapentin-macrogol 4000 co-melted, gabapentin is present in polymorph II form. The hydrate form is not detectable.

Figure 17 : FT-RAMAN spectra (in descending order)
Gabapentin polymorph II standard
Gabapentin hydrate standard
Gabapentin granulate batch 035/03

Thermo
ELECTRON CORPORATION

Il Campione Gabapentina Granulata Lotto 035/03 ha portato al seguente risultato:

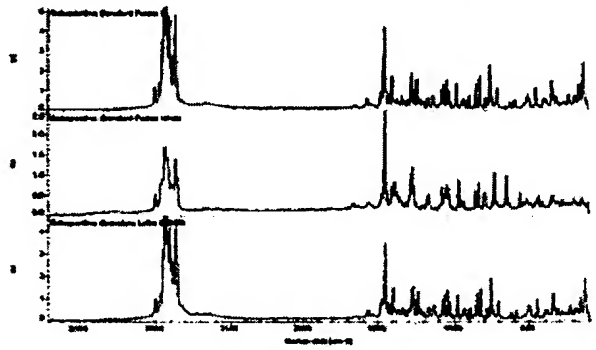


Figura 5

Ingrandendo nella zona compresa tra i 1300 e i 250 cm^{-1}:

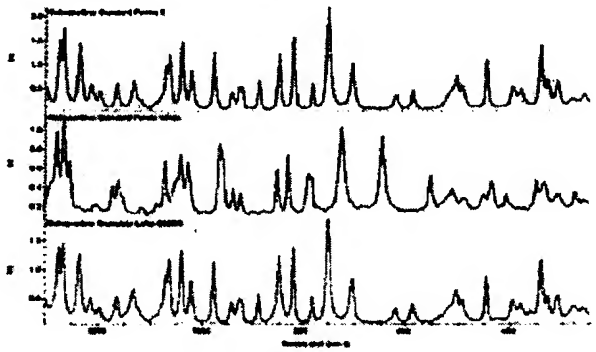


Figura 6

Dai precedenti spettri Raman si può supporre che, nel Campione Gabapentina Granulata Lotto 035/03, la Gabapentina è presente nella Forma II, mentre la Forma Idrata è non rilevabile.

On the basis of the preceding Raman spectra it may be concluded that in the granulate gabapentin is present as polymorph II and that the hydrate form is not detectable.

7. Wet granulation preliminary trials

Aim of the research

Evaluating the applicability of a wet granulation process to gabapentin in order to obtain a semifinished product with the following properties:

- keeping Form II after a granulation process with water
- absence of active ingredient degradation products
- sliding and compressing granulate

Methods

Several granulations were carried out by fast rotogranulator (Zanchetta RotoJ) using 1 Kg of gabapentin in accordance with a matrix pattern as reported in Table 1.

Trials were carried out by varying the amount of granulation water and temperature of the rotogranulator boiler during the drying phase.

Table 1. Amount of water and boiler temperature used in granulates preparation.

Water/T	**100g**	**200g**	**300g**
60°C		015/03 batch	016/03 batch
70°C	017/03 batch	018/03 batch	019/03 batch
80°C	020/03 batch	021/03 batch	

Besides trials reported in Table 1, two batches (014/03 and 022/03) were prepared without adding water but by being processed in fast rotogranulator with boiler temperature of 60 and 80°C, respectively.

These latest two trials are aimed to evaluate the effect of temperature alone on gabapentin.

Process parameters common to all trials are reported in Table 2

Table 2. Process parameters used during granulation.

Parameters	Mixing	Granulation	Drying	Cooling
Time (min)	1	10	45	15
Blade Speed (rpm)	50	300	50	50
Shatter Speed (rpm)	0	1400	0	0
Spray (psi)	0	75	0	0

The following investigations were carried out on granulates:

- purity of the active ingredient after granulation by HPLC analysis [omissis];
- residual humidity by direct titration with Karl Fisher method;
- polymorphism assessment by FT-Raman spectroscopy: the absence of excipients allows obtaining a spectra lacking signals unrelated to gabapentin. This technique was selected in that it is not sensible to particle size of the substance which is to be analyzed. As comparing data, an analysis was performed on a Neurotin 800 mg milled tablet in order to verify crystalline solid state of gabapentin currently on the market.

Results

FT-Raman analysis of granulates showed that all trials, wherein gabapentin is in touch with water, resulted in the formation of a hydrated crystalline form.

Temperature alone was not able to promote changes in crystalline structure, in the tested granulation conditions.

The same analysis, carried out on Neurotin milled tablet, reveals that gabapentin keeps Form II even after the entire manufacturing process.

Results of FT-Raman analysis are shown in the figures identified as Figures 1-24 in this paragraph.

Results of chemical analysis are summarized in Table 3

Table 3. Results of the chemical analysis of gabapentin granulates. Data are reported in w/w percentage.

Batch	Purity	Lactam	Other Impurities	Total Impurities	Humidity
Reference specification	98.5-101.5	0.10	0.10	0.50	0.50
014/03	99.5	0.01	0.04	0.15	0.05
015/03	100.3	0.01	0.04	0.16	8.67
016/03	99.2	0.01	0.06	0.20	5.88
017/03	99.0	0.01	0.06	0.16	9.58
018/03	98.0	0.01	0.07	0.18	3.81
019/03	99.6	0.01	0.07	0.23	6.42
020/03	99.4	0.01	0.04	0.16	2.70
021/03	100.8	0.01	0.06	0.17	4.14
022/03	99.8	0.02	0.07	0.19	0.10

All impurity data are comprised in the reference specification while humidity data is higher than limit in all cases where water was added.

Batches 014/03 and 022/03, where no water was added and temperature influence was assessed, are comprised in the reference specification.

Experimental conditions

In order to test samples a Nicolet Nexus FT-Raman spectrofotomer was used. Main testing conditions are summarized in the following Table:

Spectrometer:	Nexus
Spectrometer ID:	013-143
Software	Omnic 6.2a
Number of sample scans:	256
Raman laser frequency:	9393.6416
Detector:	InGaAs
Beamsplitter:	CaF2
Mirror velocity:	0.3165
Aperture:	59.00
Number of scan points:	16672
Number of FFT points:	16384
Laser frequency:	15798.3 cm^{-1}
Interferogram peak position:	8192
Apodization:	Happ-Genzel
Phase correction:	Power spectrum
Number of points:	1868
X-axis:	Raman shift (cm^{-1})
Y-axis:	Raman intensity
Data spacing:	1.928499
Source:	Off

Tabella 1

Conclusions

Raman Spectroscopy is a technique extremely useful for the analysis of polymorphism or crystallinity of pharmaceutical samples in that measurement can be carried out without any preparation of the sample and, thus, without running the risk to modify physical state thereof. [omissis]

The observation of Raman spectra of two gabapentin polymorphic forms (Form II and Hydrated Form) allows to state that the identification of the presence, in an unknown sample, of the two polymorphs will be easy since there are remarkable spectral differences, particularly, between 1300 and 250 cm^{-1}. Obtained results are summarized in the following Table:

Batch	Form II	Hydrated Form
014/03	Yes	No
015/03	No	Yes
016/03	Yes	Yes
017/03	No	Yes
018/03	Yes	Yes
019/03	Yes	Yes
020/03	Yes	Yes
021/03	Yes	Yes
022/03	Yes	No
Spray Dried	No	No
Reference tablet	Yes	No

The Raman spectra in the following pages are those of all the prepared and tested batches (014/03 to 022/03) as well as of a gabapentin spray dried sample and of reference Neurotin tablet previously milled. Spectra are reported in the figures indentified as Figures 1 to 24 in this paragraph in accordance with indications given below:

Fig.1 and 2: gabapentin reference spectra (Form II and Hydrated Form).

Fig. 3 and 4: batch 014/03 spectra.

Fig. 5 and 6: batch 015/03 spectra.

Fig. 7 and 8: batch 016/03 spectra.

Fig. 9 and 10: batch 017/03 spectra.

Fig. 11 and 12: batch 018/03 spectra.

Fig. 13 and 14: batch 019/03 spectra.

Fig. 15 and 16: batch 020/03 spectra.

Fig. 17 and 18: batch 021/03 spectra.

Fig. 19 and 20: batch 022/03 spectra.

Fig. 21 and 22: spectra of a gabapentin sample obtained by Spray Drying.

Fig. 23 and 24: spectra of reference Neurotin tablet.

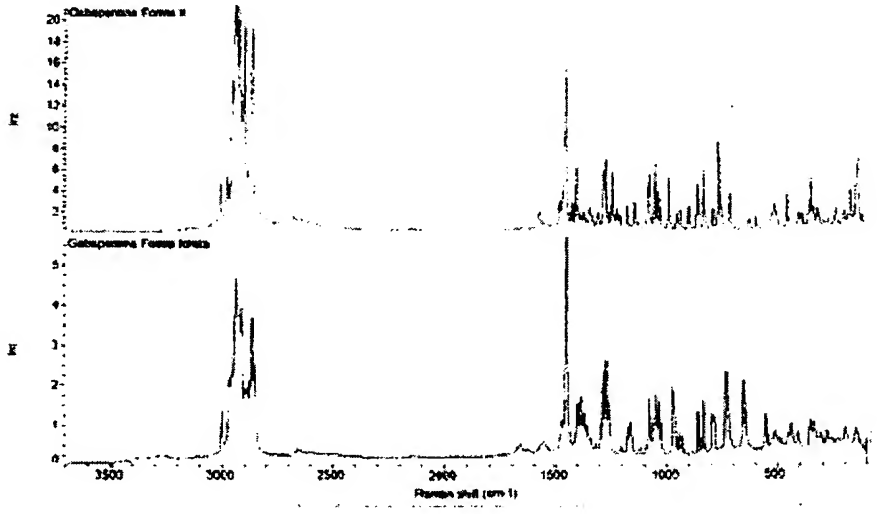


Figura 1

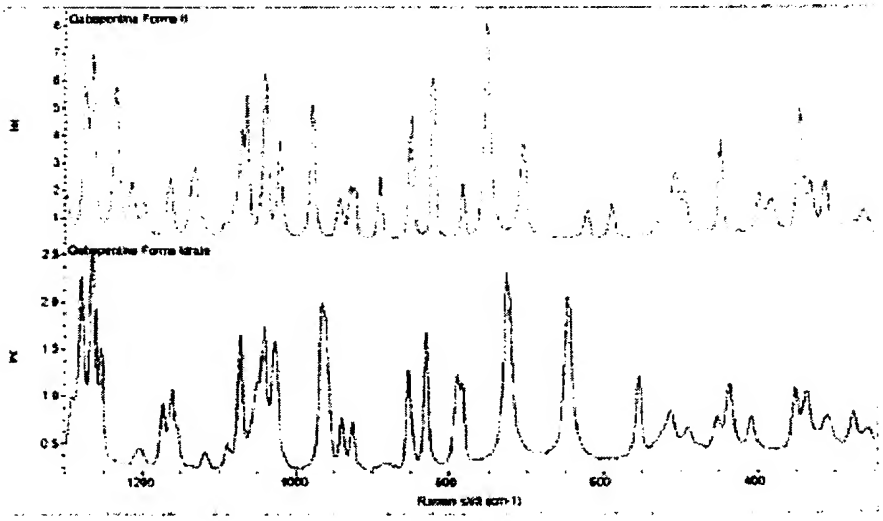


Figura 2

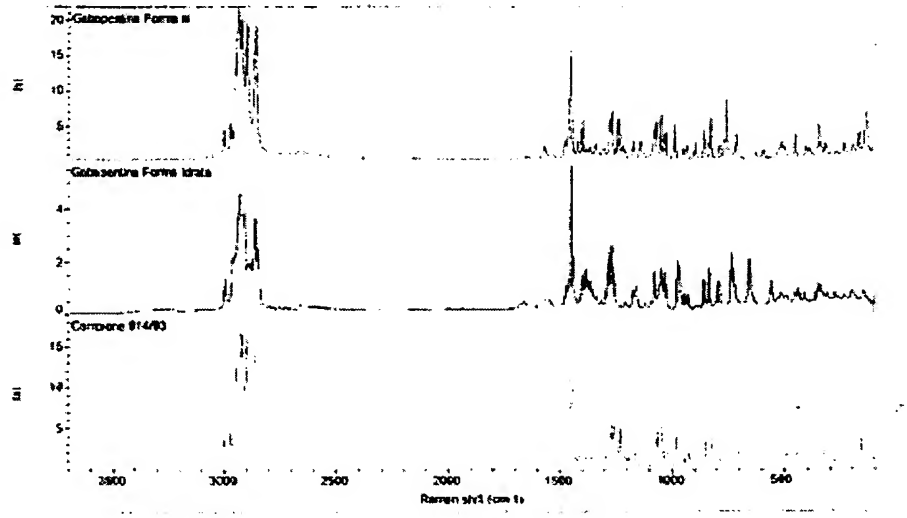


Figura 3

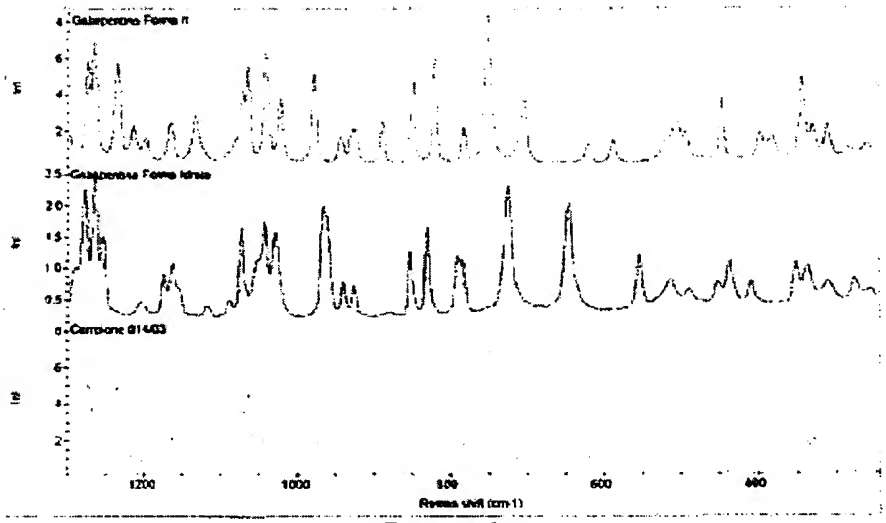


Figura 4

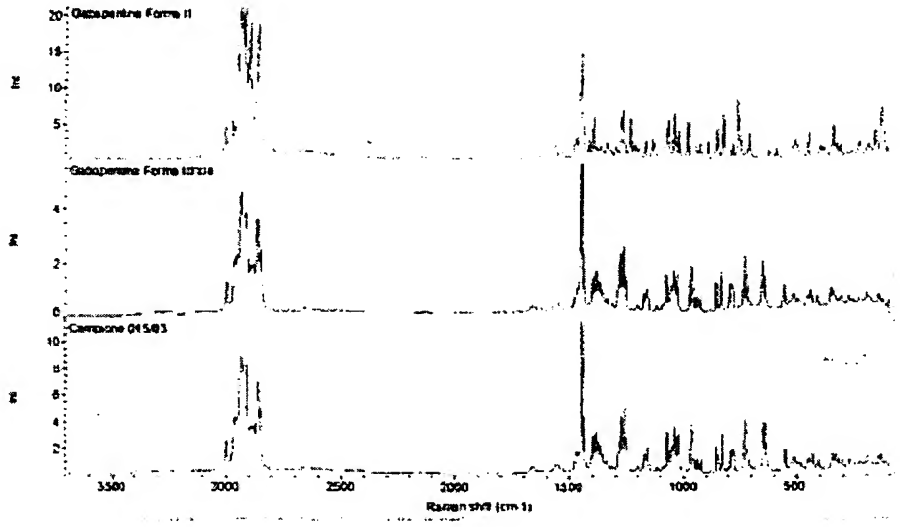


Figura 5

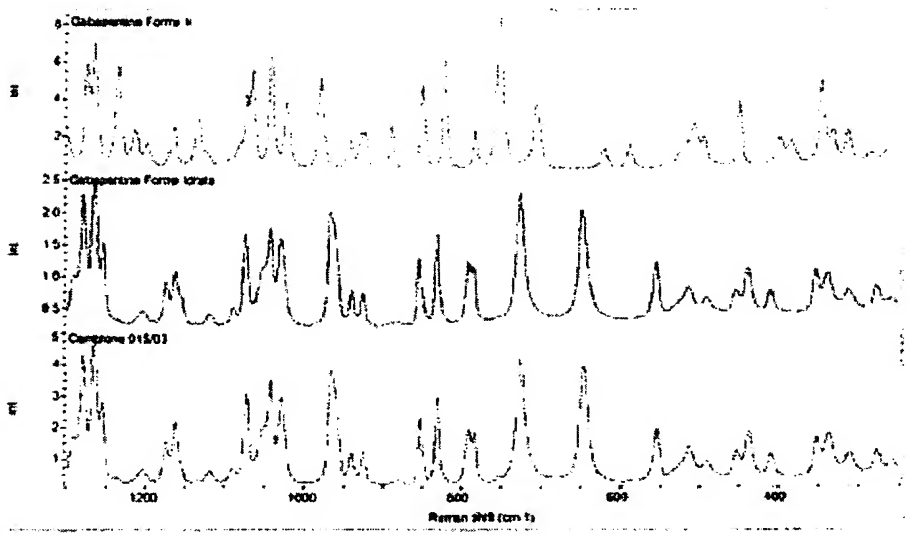


Figura 6

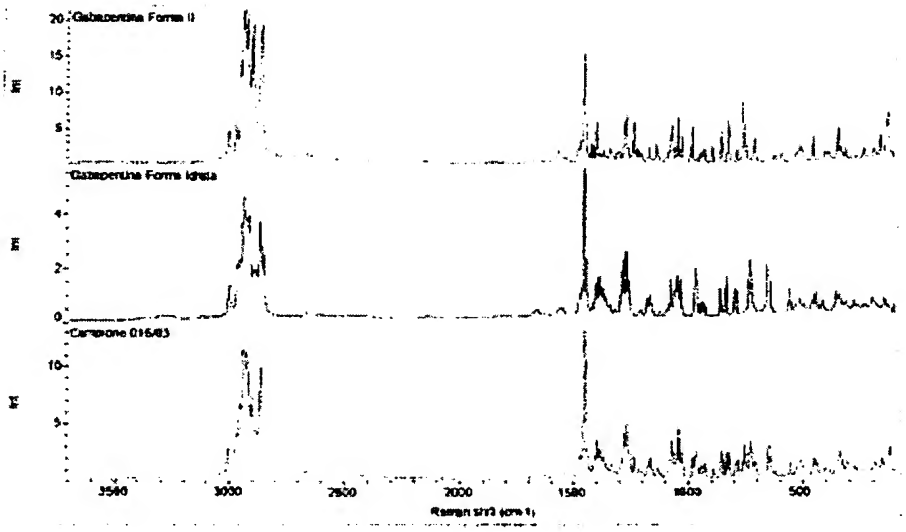
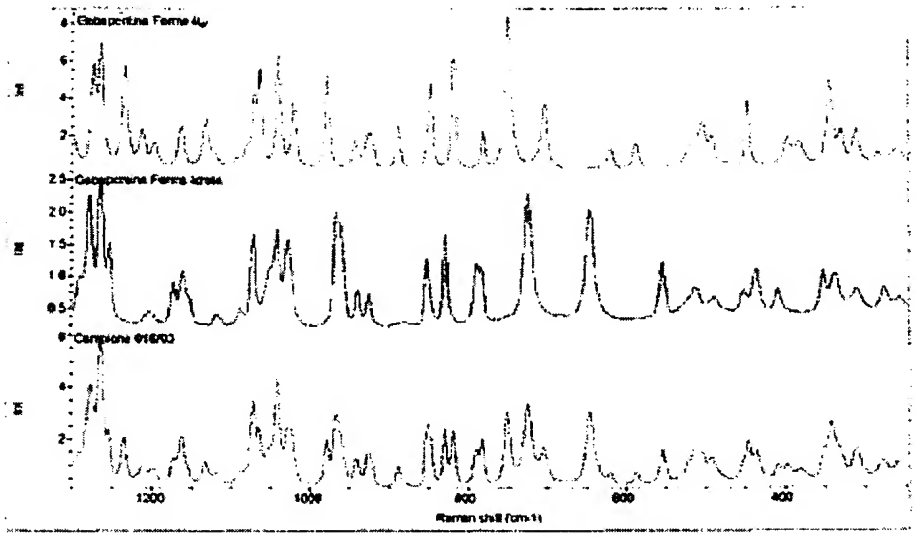


Figura 7



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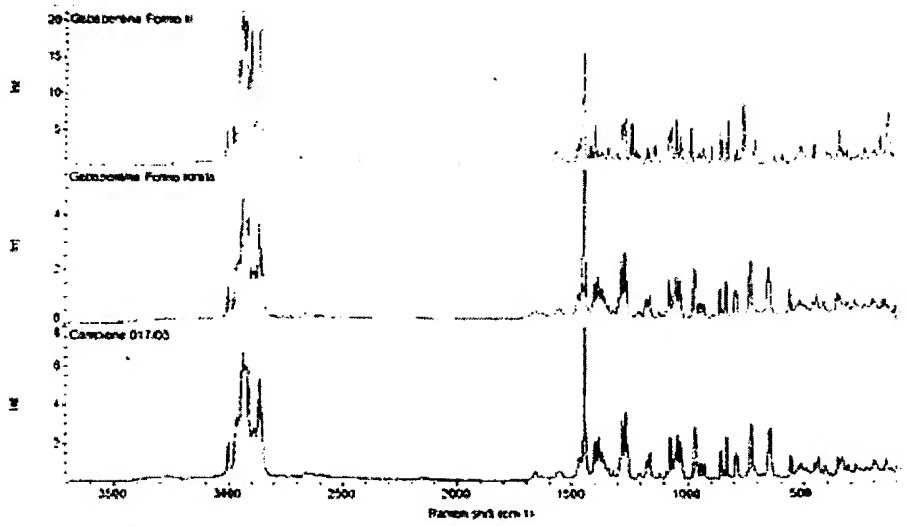

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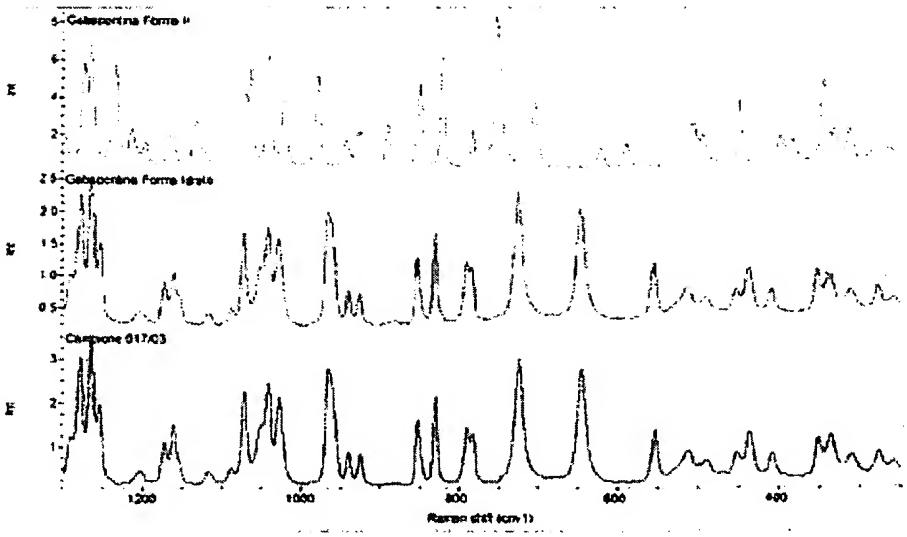
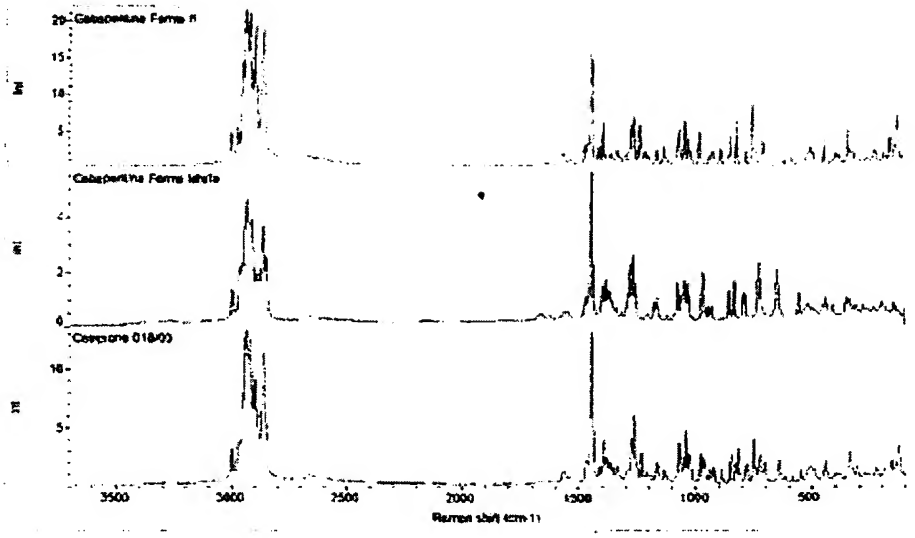


Figura 10



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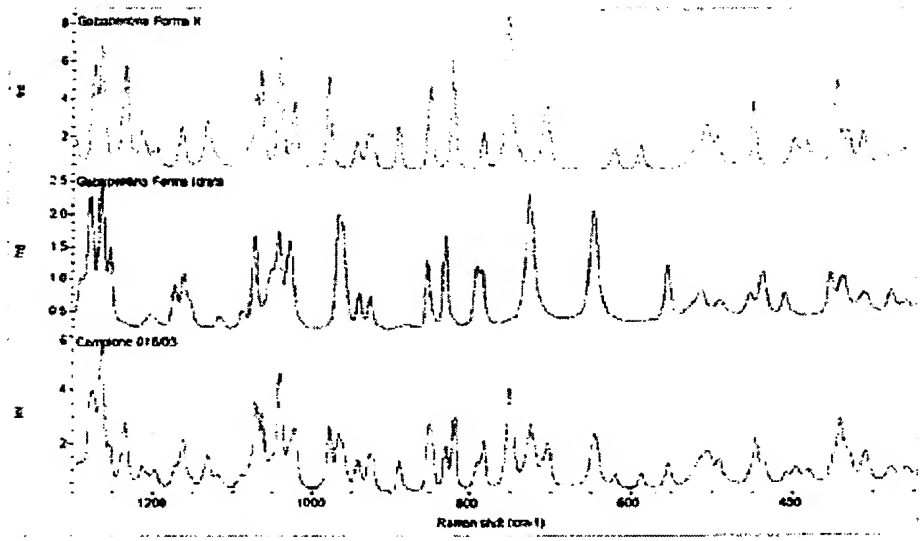

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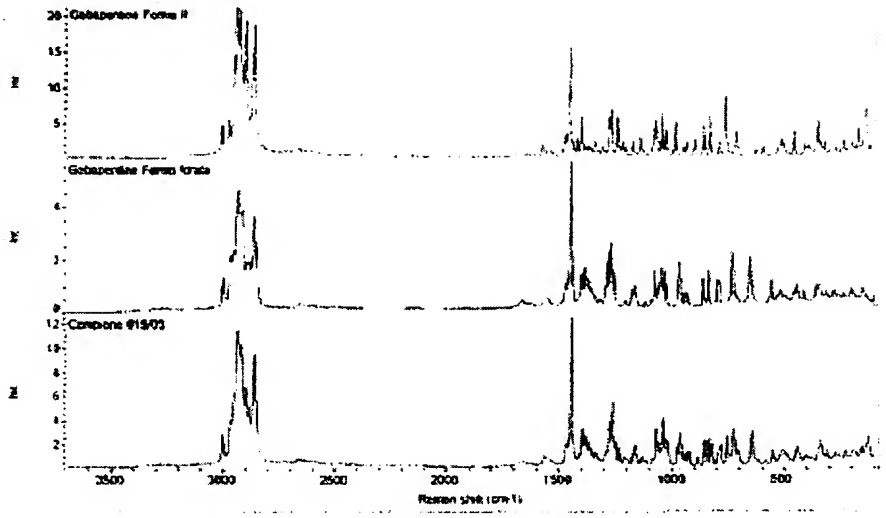

Figura 13

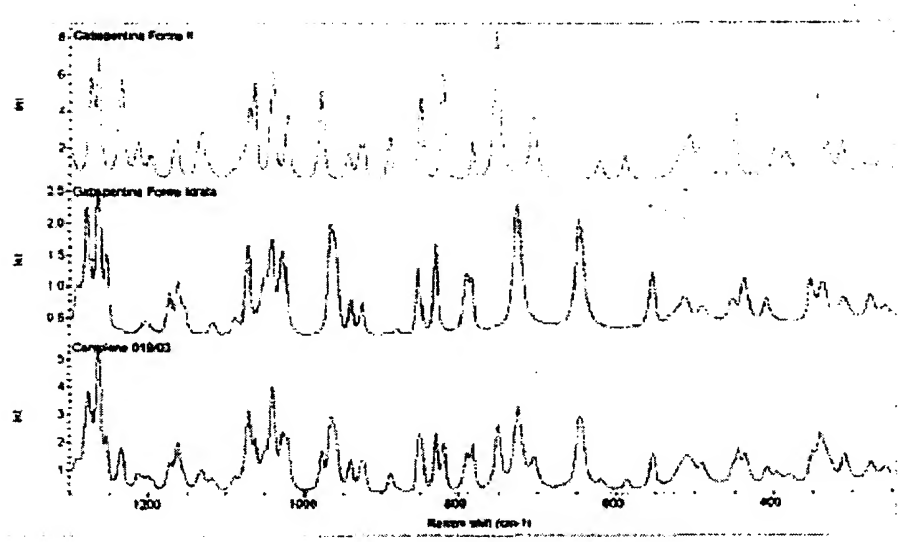

Figura 14

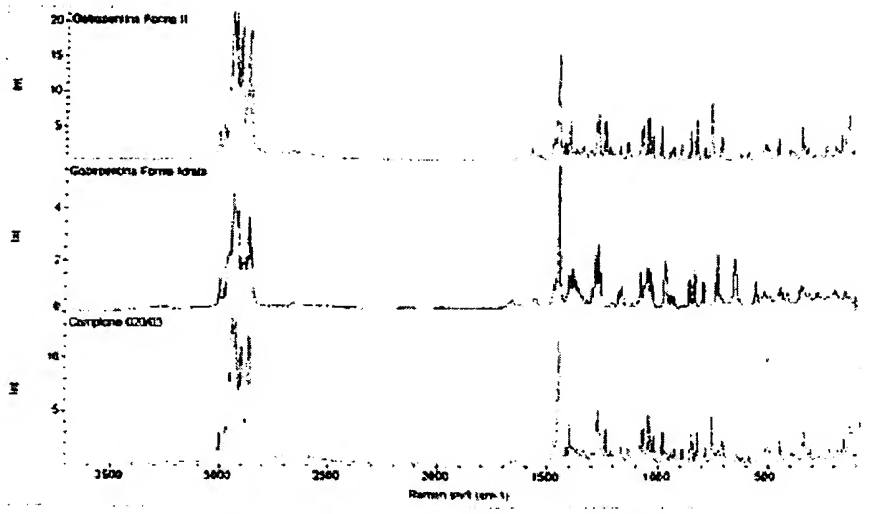

Figura 15

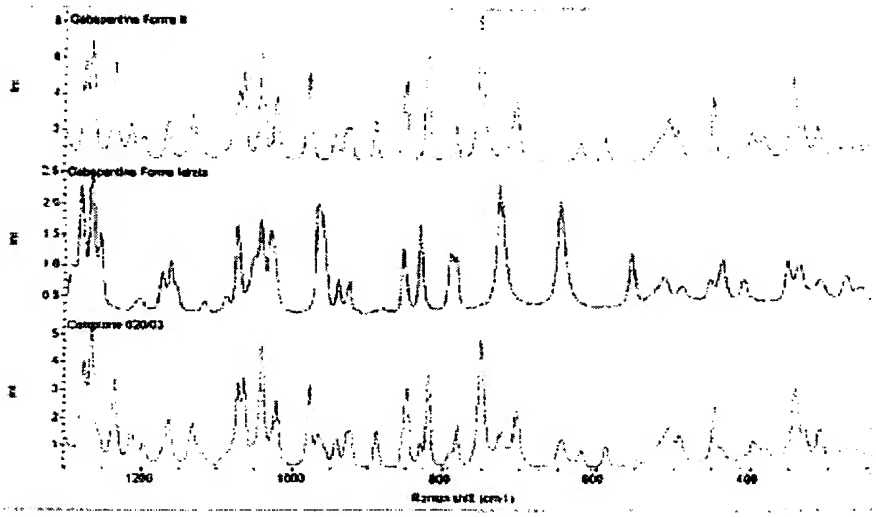

Figura 16

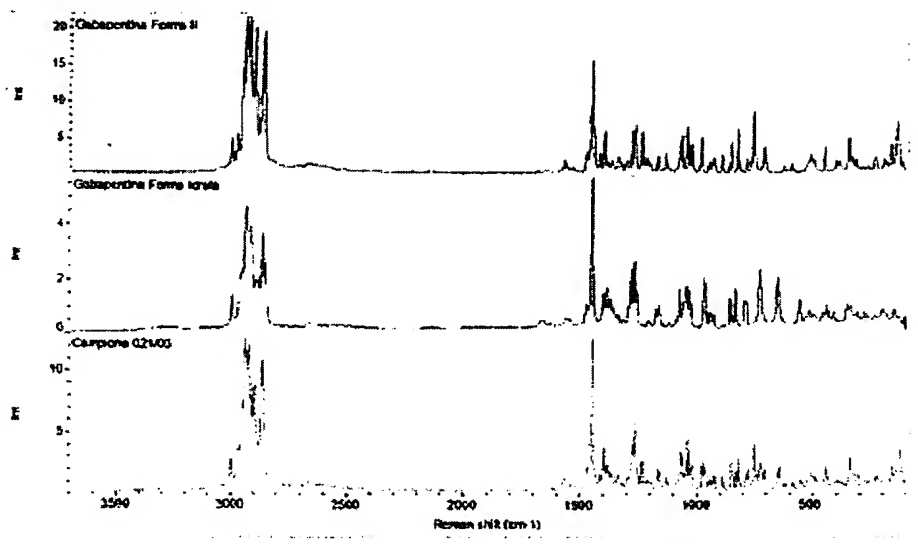

Figura 17

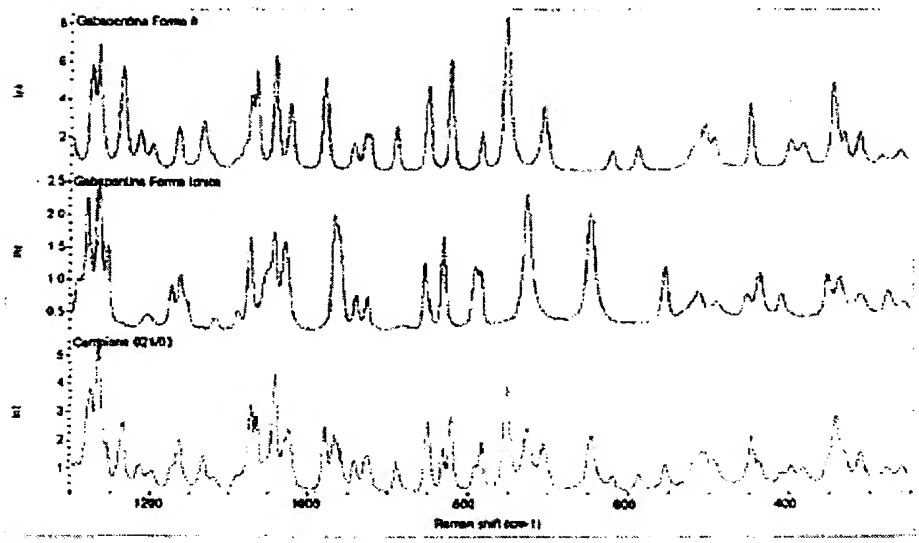

Figura 18

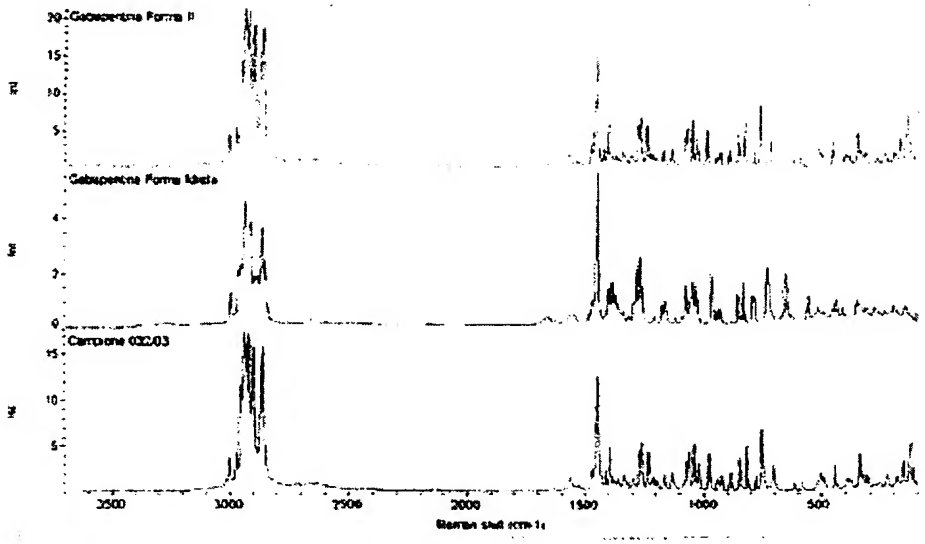

Figura 19

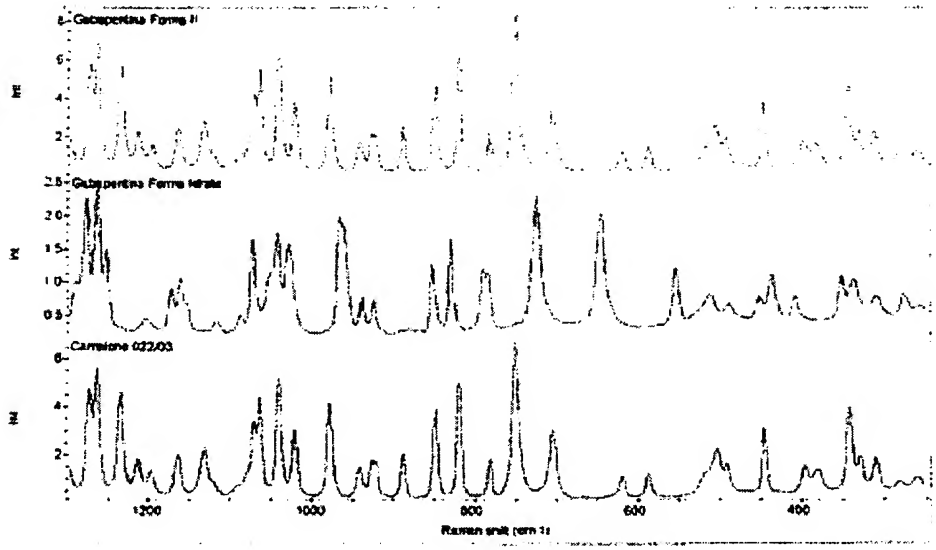

Figura 20

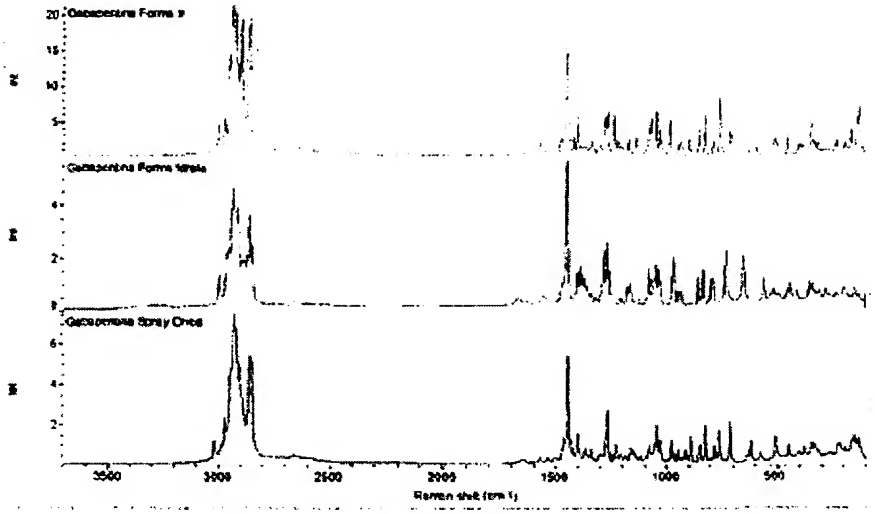

Figura 21

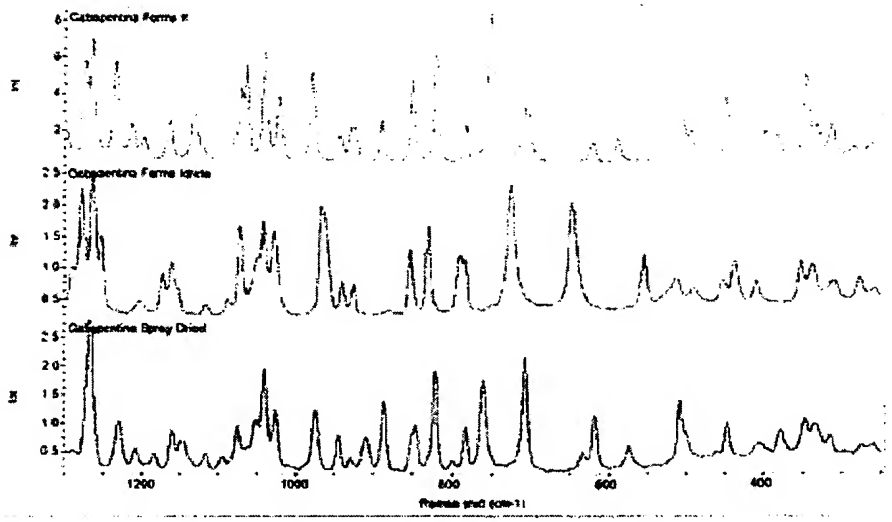

Figura 22

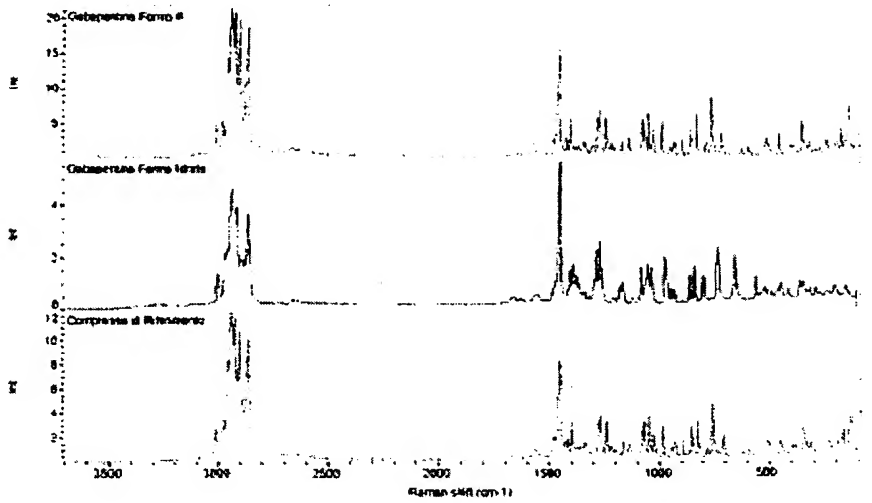

Figura 23

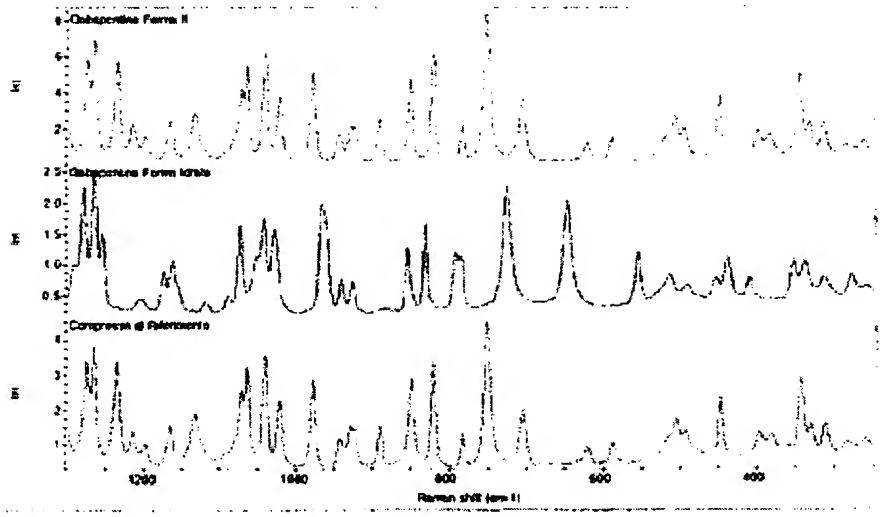

Figura 24

8. Finally, it has been further observed that compositions of the invention are able to maintain the titre of the lactam impurity below 0.2% by weight of gabapentin when subjected to standard stability test (storage conditions of 25°C with 60% of relative humidity and/or of 30°C with 65% of relative humidity). Two batches of a composition having the following ingredients in the recited amounts were prepared:

Gabapentin	88.99%
PEG 4000	4.56%
Starch, pregelatinized	4.45%
Silica, colloidal	0.50%
Magnesium stearate	0.50%

One batch was a 100 mg capsule formulations and the second batch was a 400 mg capsules formulation. The compositions were tested under the above stability conditions. Results in terms of lactam percentage by weight of gabapentin are reported in the following tables:

Batch 154/4 (400mg)	Specification	Time 0	25°C/60%U.R		30°C/65%U.R.		
			1 month	3 month	1 month	2 month	3 month
Titre (%)	95.5-105.0	99.4	100.5	101.1	99.4	101.7	100.5
Lactam (% a.i.)	≤ 0.2	0.014	0.021	0.024	0.027	0.034	0.034

Batch 165/4 (100mg)	Specification	Time 0	25°C/60%U.R		30°C/65%U.R.		
			1 month	3 month	1 month	2 month	3 month
Titre (%)	95.5-105.0	99.6	101.6	100.8	101.5	101.3	100.7
Lactam (% a.i.)	≤ 0.2	0.017	0.020	0.022	0.027	0.029	0.032

These data clearly show that the lactam content of the capsules under standard stability conditions does not exceed reference value i.e. 0.2% by weight of gabapentin. In turn, the above data demonstrates that melt granulating according to the invention allows the preparation of gabapentin pharmaceutical formulations wherein the active ingredient is particularly stable.

9. I declare further that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

10. Further Declarant saith not

Luca Rampoldi

Name:

23.07.2009

Date